PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

	Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/JP2004/004373	26.03.2004	28.03.2003

International Patent Classification (IPC) or both national classification and IPC
C07C51/36, C07C53/128

Applicant
TAKASAGO INTERNATIONAL CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Delanghe, P Telephone No. +31 70 340-4119

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

10/550564
International application No.
PCT/JP2004/004373

JC20 Rec'd PCT/PTO 26 SEP 2005

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-6
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	1-6
	No:	Claims	

2. Citations and explanations

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

Re Item V.

1 Documents

The following documents are referred to in this communication:

D1 : EP 0 544 455 A (1993-06-02)

D2 : WO 95/22405 A (1995-08-24)

2 Subject matter

Claims 1-6 define a method for producing optically active carboxylic acids using an asymmetric hydrogenation of the corresponding alpha,beta-unsaturated carboxylic acid. The reaction is done in an aqueous medium in the presence of a sulphonated BINAP-Ru complex, whereby both naphthalene portions of the BINAP are sulphonated. The sulphonated BINAP-Ru complex can be recovered and recycled in the asymmetric hydrogenation. Ee-values around 92% are obtained.

3 Novelty

Document D1 discloses (see abstract, application examples 1-3 and claims 1 and 2) the enantioselective hydrogenation of ketones, olefins and imines using the same catalyst as in the application (a sulphonated BINAP ruthenium, rhodium or iridium complex, whereby both naphthalene portions of the BINAP are sulphonated). From this, the subject-matter of independent claim 1 differs in that a different substrate (an alpha,beta unsaturated carboxylic acid) is used in the enantioselective hydrogenation.

Document D2 discloses (see abstract, page 23, line 19 to page 24, line 16 and page 28, line 18 to page 29, line 13) the enantioselective hydrogenation of 2-arylacrylic acid (specifically dehydronaproxen) using a sulphonated BINAP ruthenium complex, whereby the phenyl portions of the BINAP are sulphonated. From this, the subject-matter of independent claim 1 differs in that a sulphonated BINAP catalyst with a different substitution pattern of the sulphon groups is used (the naphthalene protion of the BINAP complex is sulphonated).

The subject-matter of independent claim 1 is therefore novel over D1 and D2 (Article 33(2) PCT).

The dependent claims 2-6 define additional features relating to the reaction

conditions of the asymmetric hydrogenation reaction. Therefore, the same line of reasoning can be followed as for the independent claim and the subject-matter of the dependent claims 2-6 is also novel over document D1 and D2 (Article 33(2) PCT).

4 Inventive step

Document D2, which is considered to represent the most relevant state of the art, discloses (see abstract, page 23, line 19 to page 24, line 16 and page 28, line 18 to page 29, line 13) the enantioselective hydrogenation of 2-arylacrylic acid (specifically dehydronaproxen) in an aqueous medium, using a sulphonated BINAP ruthenium complex, whereby the phenyl portion of the BINAP is sulphonated, yielding enantioselectivities of up to 79%. From this, the subject-matter of independent claim 1 differs in that a sulphonated BINAP Ru-complex catalyst is used which is sulphonated on the naphthalene protion of the BINAP complex, yielding enantioselectivities of up to 92%.

The problem to be solved by the present invention may be regarded as an improved process for the enantioselective hydrogenation of alpha,beta-unsaturated carboxylic acids using an easily recyclable catalyst, providing higher enantioselectivities.

For the cases of formula (2) in claim 1 for which R^1 or R^2 and R^3 are alkyl, there is no suggestion in D2 that sulphonation of a different portion of the BINAP would lead to a sulphonated BINAP ruthenium complex, which gives higher enantioselective yields in the asymmetric hydrogenation of alpha,beta unsaturated carboxylic acids.

However, it is pointed out that if the inventive step is based on a given technical effect, the latter should, in principle, be achievable over the whole area claimed (see T0939/92; OJ 1996, 309). In the present case technical effects that could potentially form the basis for the recognition of an inventive step have only been demonstrated for the compounds of general formula (2) in claim 1, for which R^1 or R^2 and R^3 are alkyl. No asymmetric hydrogenations, using the sulphonated BINAP Ru-complex catalyst, have been shown for those cases where R^1, R^2 and R^3 are an alkenyl or an aryl group. It is therefore unlikely that the variety of compounds claimed when R^1, R^2 or R^3 is alkenyl or aryl would show the same effect, since it can not be predicted what the electronic and/or steric effect of the

alkenyl or aryl groups have on the enantioselectivity of the final product. Therefore, the solution proposed in claims 1-6 of the present application is considered lacking an inventive step (Article 33(3) PCT).